

Feminization of Chronic Alcoholic Men: A Formulation

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A review of the factors historically thought to contribute to the feminization of men with Laennec's cirrhosis is presented. Objective scientific data is presented both in support of and in rejection of such factors when available. Recent hypotheses about the significance of an altered estrogen to androgen (E/T) ratio as being important in the pathogenesis of feminization also are discussed. Finally, a hypothesis which incorporates the findings of hypogonadism and cirrhosis with portal-systemic shunting is presented as a pathogenic mechanism for the feminization of men with alcohol-induced Laennec's cirrhosis.

Chronic alcoholic men frequently demonstrate evidence for hypogonadism and feminization [1]. The hypogonadism in these men is manifested by testicular atrophy, a high prevalence of infertility, loss of libido, impotence, and reduced plasma levels of testosterone. Feminization is distinct from hypogonadism and is manifested by gynecomastia, female body habitus changes, the presence of spider angiomas, palmar erythema, and changes in body hair patterns.

It has been demonstrated both clinically and in the laboratory, using a variety of animal models, that alcohol abuse *per se* in the absence of significant (irreversible) liver disease is responsible for the hypogonadism observed in alcoholic men [1–3]. Feminization on the other hand occurs later in the course of chronic alcoholism and is seen only occasionally in an alcoholic individual without demonstrable liver disease. Moreover the pathogenesis of alcohol-induced hypogonadism, although incompletely understood, particularly at a molecular level, has been shown to be due both to an alcohol-induced primary gonadal injury and to an alcohol-associated hypothalamic-pituitary dysfunction [4–6]. In contrast, the pathogenesis of the feminization of chronic alcoholic men is understood poorly if at all [1].

It is the purpose of this paper to present a historical review of the factors thought possibly to contribute to this feminization and then to present the author's own prejudice as to its pathogenesis. Clinical and experimental data used to derive the various historical hypotheses as well as the author's own prejudices will be discussed wherever possible.

This article is the seventeenth in a series entitled, "Seminars on Liver Disease," that have been presented as part of the Training Program in Liver Disease at the Veterans Administration Hospital, West Haven, Connecticut. Dr. Harold O. Conn, Professor of Medicine, Yale University School of Medicine, and Director of the Training Program in Liver Disease, is guest editor.

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The earliest proposed mechanism for the development of gynecomastia, the most obvious sign of feminization in chronic alcoholic men, was that either an estrogenic material or an inflammatory agent present in the diet of such men accumulated in the blood presumably as a consequence of reduced hepatic function [7]. Such retained material was thought to cause the breast tissue to hypertrophy and thus produce the physical finding of gynecomastia. Soon after biochemists and endocrinologists were able to isolate and synthesize individual steroids, it was demonstrated that: (a) estrogenic substances when administered to normal men could produce feminization, and (b) the liver was essential to the normal metabolic handling of sex steroids. Soon thereafter, it was demonstrated that the infusion of pharmacological amounts of steroidal estrogens could produce spider angiomas, palmar erythema, gynecomastia, and testicular atrophy both in man and in experimental animals [8–10]. Moreover, it was shown that there existed a reversible reduced hepatic clearance of estrogens in acute hepatitis [11]. As a result of these individual observations, it was proposed that feminization occurred in alcoholic men as a consequence of alcohol-induced liver disease with the resultant prehepatic retention of estrogens.

With the development of sensitive radioimmunoassay methods to directly measure the plasma levels of estrogens in man our understanding of the pathogenesis of feminization, rather than becoming clearer as a result of biochemical confirmation of increased plasma estrogen levels, became less clear as the initial reports found normal rather than increased levels of estradiol in cirrhotic men [4,11–15]. Moreover, the metabolic clearance rate of estradiol in cirrhotic men was found to be normal, not reduced [15]. Undaunted by these disturbing findings, other investigators turned to measuring the levels of weaker plasma estrogens such as estrone, while yet others began to measure levels of free plasma estradiol [13,16–18]. Although such investigations universally found increased levels of estrone, some [13] but not all [11,17,18] found increased levels of free estradiol and the matter was far from resolved. Three factors have confounded the resolution: (1) estrone has only one-fourth the biological potency of estradiol and the increases found for estrone, although definite, were not of major proportions; (b) plasma levels of sex steroid binding globulin when measured have universally been reported to be increased [4,11,14,16,19]; and (c) there are definite problems with the methodology, performance, and interpretation of studies directed at determining concentrations of free plasma steroid levels.

Despite the accumulation of such negative scientific data, the clinical observation remains that feminization occurs rarely except in alcoholics with liver disease and to an even lesser extent in some individuals with non-alcoholic cirrhosis. Thus liver disease, particularly cirrhosis, must have some pathogenic role in the development of feminization. The specific mechanism, however, has not yet been identified. Thus other approaches have continued to receive support.

A potential role for the pituitary hormone prolactin in the feminization of alcoholic cirrhotic men was proposed as soon as increased levels of this hormone were found to occur in such men [16]. The observation that such men, in addition to having increased basal levels of prolactin, also had lost the normal diurnal variation in plasma prolactin levels seemed to provide yet more credibility to a potential role for prolactin in the pathogenesis of the observed feminization [20]. Moreover, the statistically significant association between the presence of clinically apparent gynecomastia and increased prolactin levels provided additional support for such a role for prolactin [16]. Not long thereafter, however, it became apparent that prolactin is an estrogen-responsive hormone and soon the question naturally was asked whether the observed increases were primary (i.e., responsible for the feminiza-

PATHWAYS IN THE CONVERSION OF ANDROGENS TO ESTROGENS

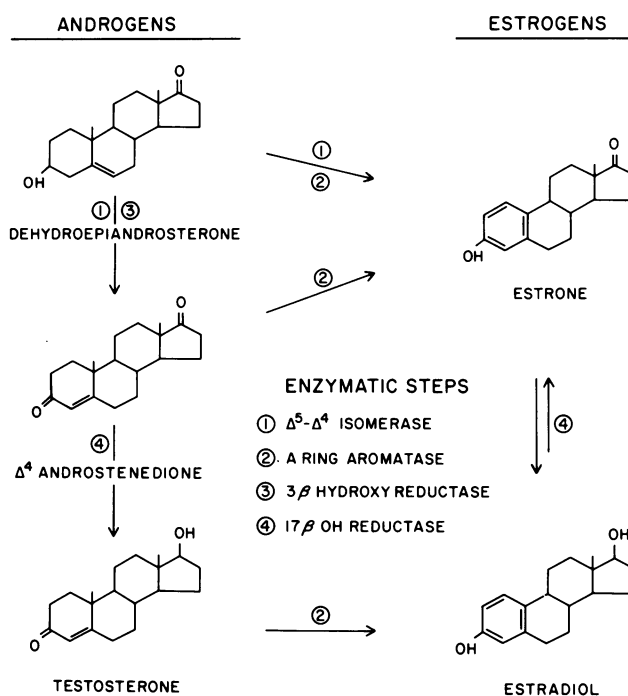


FIG. 1.

tion) or merely another secondary derivative response of hyperestrogenization (i.e., feminization) [21]. This question took on additional import as the role of prolactin in the genesis of gynecomastia came into question [22]. The present consensus among endocrinologists is that hyperprolactinemia *per se* is not capable of producing gynecomastia. This opinion is based upon the clinical observation that gynecomastia is unusual if not rare in individuals with hyperprolactinemia associated with pituitary adenoma or other neuroendocrine disease states. Moreover the gynecomastia found in association with hepatic diseases is characterized by proliferation of the stroma and ducts but not of the acini [23]. The ducts and stroma are known to be estrogen-responsive while the acini respond to progesterone and, to a lesser extent, prolactin under the influence of estrogen [24]. Gynecomastia is thought, therefore, to develop only in individuals who either have overt hyperestrogenemia or those who are exposed to weak non-steroidal estrogen agonists or androgen antagonists. Prolactin, however, may act synergistically with such materials and thereby contribute to enhanced breast hypertrophy.

With answers to resolve this dilemma not forthcoming in retrospective studies involving cirrhotic men, the possibility that feminization might occur in these men as a result of an altered estrogen-androgen ratio was advanced [13]. With the observation that in chronic alcoholic men estradiol levels are either normal or increased and that estrone levels are definitely increased while testosterone levels are reduced, it must be obvious that such a ratio would be markedly increased in alcoholic men when compared to such a ratio in normal non-alcoholic men. This hypothesis, however, has theoretical if not real problems in its general application to the problem

of feminization of alcoholic men. Clinically older men (above 60 years of age) have reduced testosterone production and plasma levels as well as normal to increased levels of estrogens and therefore an abnormally increased estrogen to androgen ratio. They are, however, not feminized as a group. At a more scientific or theoretical level, steroid receptors, be they estrogen or androgen receptors, respond to concentrations of individual steroids, not to ratios of steroid. They are quite species specific. Thus androgen receptors recognize androgens but not estrogens while estrogen receptors recognize estrogens but not androgens. Therefore, when the calculated estrogen/androgen ratio is composed of a minimal to moderate increase in the numerator (estrogen) and a moderate to marked decrease in the denominator (androgen) it is quite problematical as to whether or not such a ratio has any real biological significance in terms of increased feminization.

With all of the preceding negativism it is not unreasonable at this point to ask what then does the author think might be a reasonable explanation for the observed feminization in chronic alcoholic men. Before stating my own prejudice I would like to provide the reader with some background information. Recent studies and several clinical observations suggest that a degree of adrenal-cortical hyperactivity exists in chronic alcoholic men [25–31]. Therefore, an increased incidence of Cushing's syndrome and increased plasma levels of androstenedione, a weak androgen principally of adrenal cortical origin, have been reported to occur in chronic alcoholics. Moreover, adrenal androgens such as androstenedione and dehydroepiandrosterone are capable of being aromatized in a variety of tissues such as skin, fat, bone, muscle, brain, and liver to estrogens, particularly estrone and to a lesser extent estradiol [32–37]. Such peripheral aromatization is known to occur in normal men and has been shown to be increased in chronic alcoholic men, particularly those with cirrhosis [38,39]. Thus, peripheral aromatization of such weak adrenal androgens secreted in excess by alcoholic men would maintain normal to only moderately increased levels of such androgenic steroids while maintaining normal estradiol and increased estrone levels in men with gonadal atrophy. Such a formulation is consistent with the normal metabolic clearance rate and increased plasma production rate of androstenedione as well as the normal metabolic clearance and increased plasma production rates for both estrone and estradiol reported in cirrhotic men [15,26,29–31]. Thus, it has been demonstrated that an increased peripheral conversion of testosterone and androstenedione to estradiol and estrone, respectively, can account for at least 60 percent of the plasma level of each of these estrogens in cirrhotic men [30].

It is well known that cirrhosis, particularly Laennec's cirrhosis due to chronic alcohol abuse, is associated both with testicular atrophy and with portal hypertension and the development of portal systemic shunts. In addition it has been demonstrated that steroids, once cleared from plasma, normally undergo an enterohepatic circulation. Putting all of these rather diffuse observations together, I would propose that alcoholic men with cirrhosis clear the plasma of estrogens and androgens as well as normal individuals and further, that these hepatically extracted steroids are conjugated and then excreted not only into blood for ultimate urinary excretion but also into bile where they gain access to gut. Once within the gut these steroids are deconjugated and reabsorbed. Normally such reabsorbed steroids are rapidly removed from the portal venous blood by the liver and are reexcreted into bile without altering systemic steroid levels. However, in the individual with cirrhosis and hypogonadism due to alcohol-induced gonadal injury as well as portal hypertension with portal-systemic shunting either around or through the liver, such reabsorbed steroids gain access to the systemic circulation and therefore contribute to the

systemic levels of these steroids, thus maintaining systemic estradiol, estrone, and androstenedione levels at normal to moderately increased levels despite advanced gonad failure and reduced production rates. Such reabsorbed steroids are either then capable of directly acting at peripheral tissues as estrogens (estrone and estradiol) or can be converted, as in the case of androstenedione, to an estrogen (estrone). Such peripheral intracellular conversion of androstenedione to estrone can occur without even altering systemic plasma estrogen levels. Such a formulation is at least consistent with the observation of similar plasma levels of estradiol in cirrhotic men who have gynecomastia when compared to cirrhotic men without gynecomastia [1,4,14,22,27].

Preliminary studies in our laboratory using the rat model of chronic alcoholism are consistent also with such a formulation [40]. Specifically, alcohol feeding has been shown to be associated with increased plasma levels of corticosterone suggesting increased adrenal-cortical secretory activity as compared to ad lib fed animals. In addition, animals with artificially produced portal hypertension and presumed portal systemic shunts as a consequence of partial portal vein ligation have increased plasma levels of estrone (which presumably arises as a result of peripheral conversion of androstenedione) whether or not they are fed alcohol [40]. Thus the combination of alcohol feeding and the development of portosystemic shunts due to partial portal vein ligation in male rats is associated with the finding of increased adrenal-cortical secretory activity, manifested by increased corticosterone and presumably androstenedione levels as well as increased estrone levels, normal estradiol levels, and reduced testosterone levels.

Finally, additional studies actively in progress in our laboratory suggest that the net effect of reduced gonadal androgen production with resultant reduced plasma levels of testosterone and increased estrogen levels due to peripheral conversion of weak adrenal androgens to estrogens may alter tissue sensitivity to estrogens [41-43]. Because the combination of hypogonadism and hyperestrogenization frequently occurs in individuals with alcohol-induced liver disease but rarely in other forms of chronic liver disease, the presence of these two phenomena together in individuals with Laennec's cirrhosis may explain the frequent finding of feminization in such individuals but not in individuals with other equally advanced liver disease not associated with gonadal injury.

The ease with which all of the available data accumulated by investigators in different laboratories can be incorporated into a formulation which incorporates an altered enterohepatic circulation of biliary excreted steroids as a result of portal hypertension and primary liver disease makes it an attractive working hypothesis. Clearly, much more work will be needed either to validate or reject such a formulation. Until such data is available, however, it seems a likely candidate as an accurate explanation for the feminization in alcoholic men with cirrhosis.

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